Review Article

Serum creatinine: advantages and pitfalls

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Abstract: Serum creatinine (sCr) is today the most commonly used marker to estimate glomerular filtration rate (GFR). However, measuring and interpreting creatinine is not so simple. Some physiological reasons, particularly its dependence on muscle mass makes sCr an imperfect biomarker of GFR. However, there are also analytical reasons that could be further improved. The implementation of ID-MS traceable creatinine assays (enzymatic and compensated Jaffe) improved estimation of GFR by reducing bias. Enzymatic methods which are more precise and less susceptible to interfere with non-creatinine chromogens than compensated Jaffe methods, provide more reliable estimations of GFR.

Keywords: Creatinine; imprecision; bias; biological variability

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Introduction

In clinical practice, the use of exogenous markers to assess glomerular filtration rate (GFR) is technically complex and expensive. As a result, GFR is estimated from serum creatinine (sCr) level (1). Today, measuring sCr on automated analytical platforms has become easy, rapid and relatively inexpensive. In addition, sCr-based estimated GFR (eGFR) are automatically reported by laboratories in many countries (2,3). In all these equations, sCr is the most important variable and there is an exponential relationship between sCr and eGFR. As a result, errors in sCr measurements could significantly affect eGFR results, particularly for low sCr values that correspond to high GFR estimates (4).

In this paper, we focus on the advantages and pitfalls in serum creatinine measurement. Sources of imprecision in creatinine measurement are extra-renal and renal factors that cannot be modifiable, susceptibility to interferences and analytical errors. Analytical errors within sCr measurement consist of two types: the random error (precision) and the systematic error (bias) caused by the calibration process. Standardization of the measurement with the so-called isotope dilution mass spectrometry (IDMS) traceability has greatly reduced the bias in creatinine measurement over the last few years (4,5).

Metabolism and non-glomerular filtration rate determinants of creatinine

Theoretically an endogenous marker for GFR estimations should have the following characteristics: constant production and stable plasma/serum concentration in the absence of GFR variation; free filtration by the glomerulus; lack of secretion, reabsorption or tubular metabolism; and no extra renal elimination. Non GFR determinants of serum creatinine are linked to its metabolism and represent non-modifiable physiologic limitations. The most important

limitation from a clinical point of view is probably the variation of creatinine with muscle mass. Potential sources of error can be divided into renal and extra-renal factors

Extra-renal factors

Creatinine is an end-product of muscle catabolism of creatine. For a given individual, creatinine production is relatively stable and mainly depends on muscle mass (6). Therefore, any physiological changes in muscle mass will cause a variation in the creatinine pool independently of any GFR changes.

That is why sCr should be interpreted with caution in children and the elderly (7,8). Several sCr based equations have been built taking into account these physiological factors (age, gender and ethnicity) to estimate GFR. The most widely used for adults (between approximately 20 and 70 years old) is the chronic kidney disease epidemiology collaboration (CKD-EPI) equation (3). Equations specific to children (Schwartz equation) (8), and older adults [Berlin Initiative Study 1 (BIS1) equation] (9) have been proposed. More recently, a full age spectrum (FAS) equation, based on the concept of age-/sex-specific healthy population-normalized serum creatinine, has been developed to remediate a shift in eGFR when people are moving from one equation recommended for their age to another (10).

In addition, extreme loss (11,12) or gain in muscle mass (13,14) makes difficult the use of sCr as a marker of renal function. For example, in athletes, sCr-based eGFR may be questionable (13,15) since commonly reference intervals used are the same as in healthy population. In this population, abnormal elevated creatinine levels could be found sometimes with rugbymen generally exhibited the highest sCr following by triathletes, cyclists and soccer players (15) The indexation of eGFR to body surface area (BSA) of 1.73 m² could also explained the low reliability of creatinine-based equations in athletes and the correction of creatinine based equation with the real BSA could help to avoid a misestimation of renal excretory function (16). Banfi *et al.* recommended therefore an individualized follow-up in athletes with serial measurement of sCr to assess any change, using sCr before the start of training and competitions as the reference value, with particular attention to the type of sport and the body mass index (BMI) (15). In the same way serum creatinine is of no value for routine monitoring of renal function in patients with inherited (Duchenne muscular dystrophy...) or acquired neuromuscular disorder (17). Dietary intake of meat is also a source of creatinine (18), which explains that creatinine-based formulas cannot be used in vegetarians (19). Short-term (20 g/day for 5 days) and long-term (3 g/day for 56 days) creatine supplementation increased serum creatinine level due to an increase in muscle creatinine concentration (20). After supplementation, creatinine concentrations were therefore within the normal range.

The determination of muscle mass is of particular importance to evaluate protein nutritional status in hemodialysis (HD) patients. In clinical practice, an accurate measure of total body composition, including lean body mass, using computed tomographic or magnetic resonance imaging, total body potassium counting or deuterium dilution techniques (21) is expensive and not always available. By contrast, creatinine kinetic is a routinely available and reliable indicator of protein nutritional status and muscle mass in HD patients. Creatinine index (CI) is defined as normalized creatinine production rate, which is equal to the sum of creatinine excretion rate (dialytic removal and urinary excretion) and metabolic degradation rate in the steady state (22). Furthermore, low CI values derived from creatinine kinetic modelling have been associated with long-term all-cause and cardiovascular mortalities in HD patients (23).

Renal factors

The elimination of creatinine (113 Da) is essentially renal. Creatinine is freely filtered by the glomerulus at a constant rate but also secreted by the tubules (10% to 40%). The tubular secretion of creatinine increases with chronic kidney disease leading to an unpredictable overestimation of GFR. This secretion is an active pathway involving several transporters. In proximal tubular cells, basolateral uptake of creatinine is especially mediated by organic cation transporter 2 (OCT2) and tubular efflux of creatinine is regulated by multidrug and toxin extrusion (MATE) efflux proteins, expressed on the apical side. These transporters could be inhibited by some drugs (24) such as trimethoprim (25), cimetidine, antiretroviral drugs (26) including some old one, but also some new anti-HIV drugs like ritonavir and cobicistat (27). They block the tubular secretion of creatinine and induce an increase in the creatinine concentration without modification of GFR.

Extra-renal excretion of creatinine is quite negligible compared to urinary excretion in patients with normal to moderate renal impairment. If GFR is reduced, the amount of creatinine eliminated through this extra-renal

route is increased.

Standardization of creatinine

In 2006, recommendations from the "Laboratory Working Group of the National Kidney Disease Education Program" (NKDEP) have been released for improving GFR estimation along with guidelines for measuring sCr (28). The laboratory working group recommended the recalibration and standardization of sCr methods in order to be traceable to IDMS (isotope dilution-mass spectrometry) reference method. They also recommended the development of a commutable reference material with a sCr target value of 88.4 µmol/L, which corresponds to an average GFR of 60 mL/min/1.73 m^2. A commutable and IDMS traceable standard reference material, the SRM 967 has been release in 2007, with sCr at two concentrations, 66.5 µmol/L and 346.2 µmol/L (29).

Since then, manufacturers have made significant efforts to improve the performances of their creatinine measurement methods. Two types of ID-MS traceable creatinine methods are currently available on the market: enzymatic assays that seems specific for creatinine and compensated Jaffe creatinine assays that are corrected to take into account the sensitivity to non-creatinine chromogens, in particular proteins of the alkaline-picrate Jaffe assay (30-32).

In the Jaffe method, creatinine forms a yellow-orange complex with picric acid in alkaline solution. The concentration of the dye formed is proportional to creatinine concentration. Different technical improvements have been performed to minimize interference from endogenous substances and improve precision (kinetic and/or rate blanked assay, compensated Jaffe). For compensated Jaffe assay, sCr results are corrected by a systematic subtraction of a constant factor (15 to 25 µM) which corresponds to the average non-creatinine-dependent signal.

Enzymatic methods can be divided into two groups based on the successive enzymatic reactions. The majority of enzymatic assays uses a reaction scheme to convert creatinine to hydrogen peroxide, with the aid of creatininase, creatinase, and sarcosine oxidase. Catalyzed by peroxidase, the liberated H_2O_2 reacts with a leuko dye to generate a colored compound. Some enzymatic methods use creatinine deiminase to convert creatinine to ammonia and N-methylhydantoin. Ammonia reacts then with alpha-oxoglutarate in the presence of glutamate dehydrogenase with oxidation of the coenzyme NADPH. The decrease of NADPH is proportional to creatinine concentration and is measured at 340 nm.

Defining analytical performance goals for serum creatinine

According to the 2014 Milan Conference of the European Federation of Clinical Chemistry and Laboratory Medicine, three sources of analytical specifications could be used to judge assays at the clinical sample level (I) clinical outcomes, (II) biological variation (BV) or (III) state-of-the-art (33). The NKDEP defined a total error goal based on a maximum 10% error obtained when GFR is estimated using creatinine formulas (28). To meet the latter, an imprecision below 8% and an analytical bias relative to IDMS below 5% are required at a sCr concentration of 88.4 µmol/L. In the context of acute kidney injury (AKI), a minimum between instrument analytical coefficient of 4% has been reported to detect AKI within a clinical network (34).

Recently, biological variation (BV) data for sCr have been updated with results from the European Biological Variation Study (EuBIVAS) (18). Using the enzymatic and alkaline picrate measurement methods, the within-subject biological BV estimates [CVi [95% CI)] were comparable [4.4% (4.2–4.7) and 4.7% (4.4–4.9), respectively]. Using enzymatic methods, the between-subject BV estimates [CVg (95% CI)] were 12.8% (10.1–17) and 10.2% (8.4–13) for males and females respectively. Using alkaline picrate methods, the between-subject BV estimates [CVg (95% CI)] were 16.7% (13.1–22.1) and 12.1% (9.9–15.4) for males and females respectively. According to these performances (18), the desirable imprecision, bias and total error for enzymatic methods should be less than 2.2%, 2.8% and 6.4%, respectively. The desirable imprecision, bias and total error for Jaffe methods should be less than 2.4%, 3.2% and 7.1%, respectively.

Specificity, bias and precision of creatinine assays

Variability in sCr results have been attributed to a lack of standardization, as well as the imprecision and the non-specificity due to interfering factors of each measuring system (4,5). Since the reference measurement procedure and reference material became available, several independent studies have evaluated the impact of IDMS standardization on performances of current routine methods for creatinine (35-39).

Bias: the systematic error

Using IDMS-traceable creatinine, it is logical to expect that, after recalibration, the equivalence of the assays' results would have improved and that sCr results could be interchangeable whatever the method used or the manufacturer. In 2008, a French study conducted by the "Société Française de Biologie Clinique" (SFBC) showed optimistic results regarding traceability and precision of enzymatic sCr assays. Indeed, the majority of enzymatic methods (12 reagent-analyzer combinations were tested) reached the total analytical error of 8% (35), whereas the compensated Jaffe methods never achieved this goal at the critical level of 74.4±1.4 µmol/L (36). In addition, most of enzymatic assays allowed accurate measurements for creatinine levels lower than 40 µmol/L (35). In 2013, using data from an external quality assessment scheme, Carobene *et al.* checked the impact of creatinine standardization in Italy (37). Only the enzymatic methods showed an acceptable bias at all creatinine concentrations and the lowest between-laboratory variability. Taken together, the data from these surveys (35-39) demonstrated that the majority of enzymatic methods reaches the analytical bias inferior to 5% as proposed by the NKDEP working group. By contrast, the so-called Jaffe IDMS traceable method still exhibited bias superior to 5%, especially for "low to normal" creatinine values

Specificity and interfering substances

Standardization does not correct for analytical non-specificity problems. The lack of specificity is a major problem for Jaffe method (28,30) since non-specific chromogens, such as ketones, glucose and protein, interfere with the reaction. Therefore, manufacturers have introduced correction factors in calibrating Jaffe methods to obtain the same values as the ID-MS reference method. Single value compensation makes the approximation that pseudo-chromogens level is a constant (30,40,41) but the level of pseudo-chromogens could not be predicted at an individual level, leading to inaccuracies. Proteins are recognized as one of the most important pseudo-chromogens. Low protein levels lead to an underestimation of sCr value when using the compensated Jaffe method due to the constant factor, which make difficult renal interpretation of creatinine in children, neonates, cirrhotic patients (12,42). A high interfering effect of glucose (29 mmol/L) was observed in an external quality assessment scheme, with differences ranging from +10 to +19 µmol/L for the Jaffe creatinine assays, whereas no difference was found for enzymatic methods at a creatinine level of 60 µmol/L (43). Bilirubin is known to negatively interfere with the Jaffe method leading to underestimation of creatinine levels. Indeed, oxidation of bilirubin to biliverdin in alkaline solutions decreases the absorbance at 510 nm (the absorbance peak of both the creatinine picrate complex and bilirubin) and increases the absorbance at 620 nm (the absorbance peak of biliverdin) (32). However, bilirubin interference in Jaffe method seems rather manufacturer-dependant. Indeed, several publications found positive or negative bilirubin interference using compensated Jaffe methods (31,44). The development of the « rate blanking » method to counteract this interference could explain this false positive interference.

Enzymatic assays, based on successive enzymatic reactions are more specific than the Jaffe's ones (45). It has been reported that bilirubin can also interfere negatively with enzymatic methods, and particularly the methods based on creatinine amidohydrolase (creatininase) (31,45). This interference may be attributable to the competition between bilirubin and the assay substrate for the H_2O_2 produced during the reaction. Using anonymized icteric sera with creatinine concentrations less than 150 µmol/L, Owen *et al.* (46) found a significant mean difference of 10.7 µmol/L between the Roche enzymatic method and a liquid chromatography tandem mass spectrometry method.

Precision: the random error

This error is linked, for example, to difference in day-to-day calibration, lot-to-lot variation, intrinsic performances of the analyzers. Comparing both methods, the analytical precision (CVa) is systematically better for enzymatic assays (18,36,38). In the French multicentric evaluation, enzymatic method has between lab imprecision ranging from 1.2% to 3.4%, whereas the compensated Jaffe methods have between lab imprecision ranging from 2.5% to 5.8% (36). More recently, CVa taken from the EuBIVAS project was 1.1% and 4.4% for the enzymatic and compensated Jaffe methods respectively. The authors highlighted that Jaffe methods never achieved requirement for imprecision based on biological variation (2.2% and 2.4% for enzymatic and Jaffe, respectively) (18).

Point-of-care creatinine testing (PoCT)

There are now increasing opportunities for measuring creatinine by PoCT devices. For this purpose, creatinine

is implemented on POCT devices that are either primarily blood gas analyzers; or not (47). Blood gas analyzers [i-STAT (Abbott), ABL (Radiometer), StatProfile (Nova Biomedical)] use enzymatic creatinine with amperometric biosensor. Most of "non-blood gas" analyzers [StatSensor (Nova Biomedical), Piccolo (Abaxis), Reflotron (Roche)] use enzymatic creatinine with different method principles for the detection.

To the best of our knowledge, no analytical performance goals have been specifically published for PoCT creatinine. However, as for creatinine measurement implemented on biochemistry analyzer at the central lab, it can be expected that analytical performances of PoCT creatinine should meet the already mentioned requirements regarding bias (IDMS traceability) and precision.

In 2010, the National Health Service (NHS) evaluated seven PoCT creatinine devices available on the market in the United Kingdom (48). Most devices had a small positive bias of 10–15% in comparison to the ID-MS method. Using the 5-day CLSI EP15A3 protocol, none of the tested POCT reached the minimum imprecision of 3.3% at the lowest creatinine concentration (70 µmol/L) ranging from 3.6% to 9%. Several single center evaluations of PoCT creatinine device have been published. It has been shown that the ABL800 and the i-STAT creatinine reach the desirable (49,50) or the minimum (51) specifications for imprecision whereas the StatSensor exhibited higher coefficients of variation between 4.5% and 12.9% (52-54). The i-STAT creatinine overestimates (51,55) whereas the StatSensor using factory calibration (52,55) underestimates plasma creatinine in comparison to the IDMS-traceable Roche enzymatic assay. The ABL800 creatinine presented excellent agreement with the IDMS-traceable Roche enzymatic assay with a small bias (49,55). The i-STAT and the ABL showed no interference from bilirubin, glucose, haemoglobin and lipids at the tested concentration (47). It has been reported that the whole-blood matrix (hematocrite, plasma water fraction, red blood cell water fraction) influences on StatSensor creatinine results (53).

Conclusions

SCr is a widely available and reliable marker of renal function when integrated in GFR predictive formula. Hence, clinicians and laboratories should be aware of pitfalls in creatinine measurement to avoid misinterpretation of renal function (56). In addition to physiological reasons that makes sCr an imperfect biomarker of GFR, there are also analytical reasons. Correct implementation of ID-MS traceability has been found for most enzymatic methods (35,36), by contrast results for the compensated Jaffe methods are less clear. In addition, analytical precision is systematically better for enzymatic assays than Jaffe methods, which also suffer from interferences with non-creatinine chromogens (57).

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